REMARKS

Claims 1, 3 and 4 are pending and rejected. Claims 2 and 5-19 are cancelled. Claim 1 is amended. Claim 20 is added. Accordingly, upon entry of the present amendment claims 1, 3, 4, and 20 are pending. Each of the rejections is addressed below.

Objection to the Drawings

The Examiner objects to Figure 2 based on the allegation that the specification fails to provide a sufficient description. Applicants respectfully disagree. Nevertheless, Applicants have amended the specification to clarify that Figure 2 is a gel that shows the results of IL-10 genotyping for five different patient samples, thereby obviating the objection. Each of the lanes represents a patient sample that was amplified for IL-10 polymorphisms: GCC/GCC, GCC/ACC, GCC/ATA, ACC/ACC, ACC/ATA, ATA/ATA. The amplified bands within each lane correspond to specific IL-10 polymorphisms present within each patient sample. Therefore, Applicants' description of the drawings is not inconsistent with the specification at page 9 because each of the IL-10 polymorphisms represents a polymorphic allele of IL-10. Accordingly, the objection to the drawings should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3, and 4, which are directed to genetic screening methods that are useful or predictive for a predisposition to Alzheimer's disease or diagnostic of Alzheimer's disease in a human subject, are rejected as allegedly lacking enablement. In support of the enablement rejection, the Examiner asserts (i) that Applicants' data fails to support Applicants' claims; (ii) that prior and post-filing art indicate that the association of -1082A of IL-10, -174C of IL-6, ApoE4 carrier or -1082A IL-1 status does not predictably correlate to a diagnosis or predisposition to Alzheimer's disease (page 9, paragraphs 2 and 3); and (iii) that undue experimentation would be required to practice the claimed methods. For the reasons detailed below, Applicants respectfully disagree and request that the rejection be withdrawn.

The Office bears the initial burden of establishing a reasonable basis to question the enablement of the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Where Applicants describe methods of making and using the invention, Applicants'

specification **must** be accepted as providing an enabling disclosure unless the Examiner has evidence showing that **the truthfulness of such statements is in doubt**. M.P.E.P. 2164.04 "Burden on the Examiner under the Enablement Requirement" Specifically, the M.P.E.P. states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement of** 35 U.S.C. 112, **first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support.

Not only must the truth of Applicant's statements be in doubt, but the Examiner must provide evidence to show why the Examiner doubts the veracity of Applicants' specification.

> **[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence** or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need to go to the trouble and expense of supporting his presumptively accurate disclosure. *In re Marzocchi* 439 F.2d 220, 224 (Emphasis added.)

In support of the enablement rejection, the Examiner asserts that the correlation between -1082A IL-10 alone and -174C IL-6 alone does not correspond to the patient population that was tested. Specifically, the Examiner states, "The specification does not teach predictably associating the -1082A of IL-10, -174C of IL-6, APOE4 carrier or -1082A IL-1, alone or in combination with diagnosis or predisposition to AD in any human (Office action mailed November 4, 2008, page 8, second full paragraph)." Applicants respectfully disagree.

I. IL-10A and IL-6C alleles are associated with Alzheimer's disease

Applicants have determined that an impaired IL-10 response to the presence of ß-amyloid is a feature of Alzheimer's disease (Abstract, and page 16, first and second full paragraphs). An impaired IL-10 response is strongly implicated in the production of ß-amyloid plaques. Amyloid plaques are an indisputable diagnostic of Alzheimer's disease (page 8, third paragraph). However, the presence of plaques can only be assessed post mortem (page 8, third paragraph). There are numbers of theories explaining the accumulation of ß-amyloid in Alzheimer's disease, but the definitive mechanism has not been established (page 2, lines 1-5, page 5, last paragraph, to page 6, first paragraph). Applicants' data suggest that a subject's

inability to produce IL-10 in response to ß-amyloid is likely to aid ß-amyloid accumulation and thereby contribute to Alzheimer's disease pathology (page 6, last paragraph, to page 7, last paragraph). It is assumed that ß-amyloid in normal individuals is simply metabolized and that IL10 response plays a significant role in preventing ß-amyloid accumulation. The presence of low levels of IL-10 in response to disease specific antigen in such patients is highly indicative of a susceptibility to Alzheimer's disease (Abstract). The data provided in Applicant's specification are from actual Alzheimer's patients and healthy age-matched controls. These data show that the age-matched healthy controls were high IL-10 producers (page 16, first and second paragraphs). In contrast, not only were the low producers suffering from Alzheimer's disease, but the disease onset started at an earlier age and progressed faster (page 16, first and second paragraphs). This clearly shows that elevated levels of IL-10 prevent the occurrence of Alzheimer's disease or ameliorate the progression of the disease (page 28, paragraphs 1-4).

Table V addresses the frequency of IL-10 genotypes and alleles in Alzheimer's disease patients and healthy control patients (page 25, first paragraph). Table VI addresses the frequency of IL-6 genotypes and alleles in Alzheimer's disease patients and healthy control patients (page 26, first paragraph). The patients used to complete this analysis are described at page 22, paragraphs 1-3, and page 23, first paragraph, where Applicants teach that 65 Alzheimer's patients and 65 healthy control patients were used for genotyping. The sequence of IL-10 and IL-6 was assayed at polymorphic positions using PCR-sequence specific primers and ApoE genotype was assayed using restriction digest (page 23, second paragraph). Applicants found that Alzheimer's disease patients showed a higher frequency of the -1082A low producer allele (page 24, second paragraph). Furthermore, Applicants found that the presence of both IL-10A and IL-6C alleles significantly raised the risk of developing Alzheimer's disease (page 26, last paragraph). In sum, Applicant's have clearly demonstrated an association of IL-10A and IL-6C alleles with Alzheimer's disease.

The Examiner is concerned about the number of patients that were assayed, suggesting that 126 patients with Alzheimer's disease were analysed because in Table V the sum of A (90) and G (36) alleles is 126 (page 8, Office action mailed November 4, 2008). This is incorrect. Human cells are diploid, i.e., each cell contains two of every chromosome, and a subject's genotype is analysed at a pair of alleles present on each of the subject's two chromosomes.

Accordingly, 63 of the patients with Alzheimer's disease were analysed at an allele present on each chromosome, resulting in a total of 126 alleles analysed. Regarding these results, Applicants state that "The main finding of this study was the identification of a group of subjects with a high risk of late-onset AD on account of the concomitant presence of IL-10 -1082A and IL-6 -174C alleles (page 29, second full paragraph). Thus, contrary to the Examiner's assertion at page 8, last paragraph, Applicants' specification clearly associates Alzheimer's disease with IL-10 -1082A and IL-6 -174C alleles. Therefore, this basis for the rejection should be withdrawn.

II. The prior art supports Applicants' disclosure

The Examiner indicates that it is unpredictable whether a particular polymorphism is associated with Alzheimer's disease. In support of this assertion, the Examiner cites Bagnoli et al. (Neuroscience Letters 418:262-265, 2007; hereinafter "Bagnoli") and Capruso et al. (Experimental Gerontology 39:1567-1573, 2004; hereinafter "Capruso"), which allegedly conflict with the data presented in Applicant's specification (Office action mailed November 4, 2008, page 9, fourth full paragraph).

Although Bagnoli and Capruso present findings that purportedly differ from the findings described by Applicants, Bagnoli and Capruso fail to provide "reason to doubt the **objective truth** of the statements contained" within Applicant's specification as required to support the enablement rejection. M.P.E.P. 2164.04 In fact, Bagnoli and Capruso acknowledge that their results may not be definitive and that there are a number of factors that could cause their results to differ from those present in the prior art. For example, Bagnoli states:

> Three studies carried out on Italian and Chinese populations have shown that IL10 polymorphisms are a genetic risk factor in the development of AD, demonstrating that IL10 -1082A, 0819T and -592A alleles are significantly over represented in AD patients compared to non-demented controls. However, other studies have not been able to replicate these results and it has been suggested that **the role of the IL10 gene in AD susceptibility may be limited to certain populations, indicating the need of further studies** (page 262, right column, lines 14-22; emphasis added).

Similarly, Capurso acknowledges that "regional European differences in genotype and allele frequencies of the Il-6-174 g/c promoter polymorphism may explain in part controversial findings on this polymorphism in AD in various European studies (Abstract)." Capurso does not regard the published findings as definitive, but suggests that "further studies on larger and different populations, controlling for ethnic and geographic variability" should be conducted to explore regional variations in IL-6 genotype and allele frequencies (page 1572, right column, last paragraph).

Although the Examiner acknowledges that Applicant's have shown a statistically significant correlation between -1082A IL-10 and Alzheimer's disease, the Examiner nevertheless asserts that the association of -1082A of IL-10, 174C of IL-6, ApoE4 carrier or -1082A IL-1 with Alzheimer's disease is unpredictable because "the specification does not teach a large sample size, analyze different ethnic groups or provide confidence levels greater than 95% for 1082A of IL-10, 174C of IL-6, ApoE4 carrier. Although large sample size studies are of interest in the epidemiology of any human disease, in clinical genetics there is an increasing drive to identify particular genetic variations that correlate with disease in particular sub-populations. The finding that a particular marker has been positively associated with disease in a small sample of carefully and closely matched individuals is not negated by contrary observations in a large population of unmatched individuals. Applicants have discovered that certain patients that have -1082A IL-10 are at an increased risk for developing Alzheimer's disease, and that use of -1082A IL-10 together with other Alzheimer's disease markers (e.g., 174C of IL-6, ApoE4 carrier or -1082A IL-1) is likely to be usefully in assessing a subject's Alzheimer's disease risk. In view of these results, Applicants have fully enabled the claimed subject matter regardless of whether or not the marker is useful for predicting Alzheimer's risk in **every** subject.

In contrast to the Bagnoli and Capruso, Applicants have provided literature that confirms the studies upon which the Applicants' claimed invention is based (References submitted with Response filed July 15, 2008). In particular, the scientific publications cited by Applicants indicated that the gene polymorphisms presently claimed are indicative of the presence or absence of a predisposition to develop Alzheimer's disease. See, for example, Combarros et al *J. Neural Transm.* **2008** Jun:115 (6) pp 863-7 (Epub 2008 Feb 26) "Aromatase and interleukin-10

genetic variants interactively modulate Alzheimer's disease risk." or SL Ma et al *Neurobiol Aging* **2005** Jul: 26(7) pp 1005-10 (epub 2004, Nov 23) "The Association Between Promoter Polymorphism of the Interleukin-10 gene and Alzheimer's disease." or Infante et al. *Neurology.* **2004**; 63: pp1135-1136 "Gene–gene interaction between interleukin-6 and interleukin-10 reduces AD risk" (Copies submitted with Response filed July 15, 2008).

Because Alzheimer's disease can only be definitively confirmed post-mortem there are considerable differences in the clinical and psychometric methods used to establish a diagnosis of Alzheimer's disease and to assess disease progression. Consequently, it is not surprising that certain differences exist between groups assaying the predictive value of various genetic markers in predicting Alzheimer's disease risk. Such differences may be attributable to variability in the clinical and psychometric methods used to assess and select patients and controls.

The M.P.E.P. cautions that Applicants' disclosure must be taken as being in compliance with the enablement requirement of **35 U.S.C. 112** in the absence of evidence to the contrary. Given that Applicants' have provided strong countervailing evidence in support of their disclosure, the Office has failed to establish a reasonable basis to question enablement. Accordingly, this basis for the enablement rejection should also be withdrawn.

In further support of the enablement rejection, the Examiner cites Kroese (Genetics in Medicine 6:475-480, 2004), Inonnidis (PLoS 2:e124, 2005), Hattersley (Lancet 366:1315-1323, 2005), and Hegele (Am Heart Assoc. 22:1058, 2002), which purportedly establish criteria for successful genetic association studies. Applicants note that although the cited references are generally relevant to the field of genetic association, none of these references is specifically relevant to methods that are useful or predictive for a predisposition to Alzheimer's disease or diagnostic of Alzheimer's disease in a human subject. Accordingly, these references fail to support the enablement rejection of the claims.

In further support of the enablement rejection, the Examiner states:

> In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to AD . . . such analysis is replete with unpredictable

> experimentation and is considered undue (Office action mailed November 4, 2009, page 14, lines 9-14).
>
> Applicants respectfully disagree. In fact in one of the currently designed confirmatory studies that applicant is planning the sample size as calculated by de l'Unité de Recherche Clinique de l'hôpital Pitié-Salpêtrière in Paris, France using SAS version 8.2 (SAS Institute, Cary, N.C.) is 168 per group.
>
> Au risque α de 0.05, le nombre de sujets nécessaire, pour démontrer l'effet du génotype de l'IL-10 avec une puissance de 0.9, est de 168 par groupe (10000 simulations sous SAS/IML). [Translation : With the α risk of 0.05, the number of subjects necessary, in order to show the effect of the genotype of the IL-10 with a power of 0.9, is 168 per group (10000 simulations under SAS/IML).]

Clearly, conducting analyses with 168 subjects is not unduly burdensome. Moreover, even if multiple comparisons are added, such sample size does not constitute undue experimentation because one of skill in the art could readily identify subjects having allelic variants present at one or more of the SNP loci at positions -1082 of the gene encoding IL-10.

The proper test of enablement is set forth in *United States v. Telectronics, Inc.*, (857 F.2d 778, 785, 8 USPQ2d at 1217, 1223 (Fed. Cir. 1988)):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

The fact that some experimentation may be required to practice the invention does not indicate that the claims lack enablement so long as the experimentation is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In Wands, the claims at issue were directed to immunoassays that required the use of monoclonal antibodies. The identification of these antibodies required extensive screening, and the court considered the question of whether undue experimentation would be required to carry out the screens. The court found that the specification enabled the claims because "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. The Wands court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

The present case is analogous to Wands in all important respects because one of skill in the art provided with Applicants' specification could readily identify subjects having a

predisposition to Alzheimer's disease by analysing a DNA bearing sample taken from the subject to determine the allelic variants present at one or more of the SNP loci at positions -1082 of the gene encoding IL-10, where a polymorphism selected from the group consisting of a G to A substitution at position –1082 is determined and the substitution is useful or predictive for a predisposition to Alzheimer's disease or diagnostic of the presence of Alzheimer's disease. The fact that some screening would be required to identify subjects having a susceptibility to Alheimer's disease does not support a lack of enablement because such experimentation is merely routine. Moreover, Applicants' specification provides considerable direction and guidance regarding how such screening should be carried out (pages 22-30).

Specifically, at pages 22-23, Applicants describe methods for screening subjects for Alzheimer's disease by extracting genomic DNA from blood samples and analysing the sequence of the IL-10 and IL-6 promoters using sequence-specific primers. Statistical analysis of genotype and allele frequencies showed that there was a higher percentage of IL-10 -1082A and IL-6 -174C alleles among Alzheimer's patients (page 28, fourth full paragraph, and page 29, second full paragraph). Provided with this disclosure, one of ordinary skill in the art would be able to make and use the invention commensurate in scope with the claims because all of the methods needed to practice the invention, including methods for genetic analysis of DNA present in a patient sample, were merely routine and were well known at the time the application was filed as evidenced by the references cited by the Examiner, which describe the analysis of IL-10 and IL-6 polymorphisms and their association with Alzheimer's disease.

The Office must provide specific technical reasons showing why one skilled in the art could not practice the invention without undue experimentation. M.P.E.P. 2164.04 In the absence of such evidence or reasoning, the enablement rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3, and 4 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants respectfully disagree with the rejection. However, without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claim 1, from which the remaining rejected claims depend, has been amended to delete "animal", thereby obviating the rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the above remarks, Applicants believes the pending application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicants respectfully request the Examiner to telephone Applicants' undersigned representative at the number below so that a telephonic interview may be scheduled. Applicants thank the Examiner in advance for this courtesy.

No fee is believed due for consideration of this response, however, the Director is hereby authorized to charge any credits or deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

By _____

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